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CASARETT AND DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS

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Toxicokinetics. Knowledge of the toxicokinetics of beryllium has largely been obtained from experimental animals, particularly the rat. Clearance of inhaled beryllium is multiphasic; half is cleared in about 2 weeks; the remainder is removed slowly, and a residuum becomes fixed in the tissues probably within fibrotic granulomata. Gastrointestinal absorption of ingested beryllium probably only occurs in the acidic milieu of the stomach, where it is in the ionized form, but passes through the intestinal tract as precipitated phosphate. Removal of radiolabeled beryllium chloride from rat blood is rapid, having a half-life of about 3 h. It is distributed to all tissues, but most goes to the skeleton. High doses go predominantly to the liver, but it is gradually transferred to the bone. The half-life in tissues is relatively short, except in the lungs, and a variable fraction of an administered dose is excreted in the urine where it has a long biological half-life. Normal beryllium excretion is on the order of a few nanograms per liter.

Skin Effects. Contact dermatitis is the commonest beryllium-related toxic effect. Exposure to soluble beryllium compounds may result in papulovesicular lesions on the skin, which it is a delayed-type hypersensitivity reaction. The hypersensitivity is cell mediated, and passive transfer with lymphoid cells has been accomplished in guinea pigs. If contact is made with an insoluble beryllium compound, a chronic granulomatous lesion develops, which may be necrotizing or ulcerative. If insoluble beryllium-containing material becomes embedded under the skin, the lesion will not heal and may progress in severity. Use of a beryllium patch test to identify beryllium-sensitive individuals may in itself be sensitizing, so any use of this procedure as a diagnostic test is discouraged.

Pulmonary Effects. ***Acute Chemical Pneumonitis.*** Acute pulmonary disease from inhalation of beryllium is a fulminating inflammatory reaction of the entire respiratory tract, involving the nasal passages, pharynx, tracheobronchial airways, and the alveoli, and in the most severe cases it produces an acute fulminating pneumonitis. This occurs almost immediately following inhalation of aerosols of soluble beryllium compounds, particularly fluoride, an intermediate in the ore extraction process. Severity is dose related. Fatalities have occurred, although recovery is generally complete after a period of several weeks or even months.

Chronic Granulomatous Disease, Berylliosis. This syndrome was first described among fluorescent lamp workers exposed to insoluble beryllium compounds, particularly beryllium oxide. The major symptom is shortness of breath, which in severe cases may be accompanied by cyanosis and clubbing of fingers (hypertrophic osteoarthropathy, a characteristic manifestation of chronic pulmonary disease). Chest x-rays show miliary mottling. Histologically, the alveoli contain small interstitial granulomata, which resemble those seen in sarcoidosis. In the early stages, the lesions are composed of fluid, lymphocytes, and plasma cells. Multinucleated giant cells are common. Later, the granulomas become organized with proliferation of fibrosis tissue, eventually forming small, fibrous nodules. As the lesions progress, interstitial fibrosis increases with loss of functioning alveoli, impairment of effective air–capillary gas exchange, and increasing respiratory dysfunction.

Carcinogenicity. Evidence for carcinogenicity of beryllium was first observed in experimental studies beginning in 1946, before the establishment of carcinogenicity in humans. Epidemiologic confirmation in humans has been evolving so that there is increasing acceptance that beryllium is in fact a human carcinogen. Studies of humans with occupational exposure to beryllium prior to 1970 were negative. However, reports of two worker populations and a registry of beryllosis cases studied earlier show a small excess of lung cancer, although the total number of cases is small. The IARC (1994) states there is sufficient evidence in humans and animals for the carcinogenicity of beryllium and its compounds.

In vitro studies of genotoxicity have shown that beryllium will induce morphological transformation in mammalian cells (Dipaolo and Casto, 1979). Beryllium will also decrease the fidelity of DNA synthesis but is negative when tested as a mutagen in bacterial systems.

Cadmium

Cadmium is a modern toxic metal. It was only discovered as an element in 1817, and industrial use was minor until about 50 years ago. But now it is a very important metal with many applications. Its main use is in electroplating or galvanizing because of its noncorrosive properties. It is also used as a color pigment for paints and plastics, and as a cathode material for nickel-cadmium batteries. Cadmium is a by-product of zinc and lead mining and smelting, which are important sources of environmental pollution. The toxicology of cadmium is extensively reviewed by Friberg et al. (1986a) and the WHO (1992).

Exposure. Airborne cadmium in the present-day workplace environment is generally 0.05 or $\mu g/m^3$ or less. Air from uncontaminated areas contains less than 0.1 $\mu g/m^3$. Meat, fish, and fruit contain 1 to 50 $\mu g/kg$, grains contain 10 to 150 $\mu g/kg$, and the greatest concentrations are in the liver and kidney of animals. Shellfish, such as mussels, scallops, and oysters, may be a major source of dietary cadmium and contain 100 to 1000 $\mu g/kg$. Shellfish accumulate cadmium from the water and then bind to cadmium-binding peptides. Total daily intake from food, water and air in North America and Europe varies considerably but is estimated to be about 10 to 40 μg per day.

Cadmium is more readily taken up by plants than other metals, such as lead. Factors contributing to cadmium's presence in soil are fallout from the air, cadmium-containing water used for irrigation, and cadmium added to fertilizers. Commercial phosphate fertilizers usually contain less than 20 mg/kg. Another source of concern about potential sources of cadmium toxicity is the use of commercial sludge to fertilize agricultural fields. Commercial sludge may contain up to 1500 mg of cadmium per kilogram of dry material (Anderson and Hahlin, 1981).

Respiratory absorption of cadmium is about 15 to 30 percent. Workplace exposure to cadmium is particularly hazardous where there are cadmium fumes or airborne cadmium. Most airborne cadmium is respirable. A major nonoccupational source of respirable cadmium is cigarettes. One cigarette contains 1 to 2 μg cadmium, and 10 percent of the cadmium in a cigarette is inhaled (0.1 to 0.2 μg). Smoking one or

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more packs of cigarettes a day may double the daily absorbed burden of cadmium.

Toxicokinetics. Gastrointestinal absorption is less than respiratory absorption and is about 5 to 8 percent. Absorption is enhanced by dietary deficiencies of calcium and iron and by diets low in protein. Low dietary calcium stimulates synthesis of calcium-binding protein, which enhances cadmium absorption. Women with low serum ferritin levels have been shown to have twice the normal absorption of cadmium (Flanagan et al., 1978). Zinc decreases cadmium absorption, probably by stimulating production of metallothionein.

Cadmium is transported in blood by binding to red blood cells and large-molecular-weight proteins in plasma, particularly albumin. A small fraction of blood cadmium may be transported by metallotheionein. Blood cadmium levels in adults without excessive exposure is usually less than 1 μg/dL. Newborns have a low body content of cadmium, usually less than 1 mg total body burden. The placenta synthesizes metallothionein and may serve as a barrier to maternal cadmium, but the fetus may be exposed with increased maternal exposure. Human breast milk and cow's milk are low in cadmium, with less than 1 μg/kg of milk. About 50 to 75 percent of the body burden of cadmium is in the liver and kidneys; its half-life in the body is not known exactly, but it is many years and may be as long as 30 years. With continued retention, there is progressive accumulation in the soft tissues, particularly in the kidneys, through ages 50 to 60, when the cadmium burden in in soft tissues begins to decline slowly. Because of the potential for accumulation in the kidneys, there is considerable concern about the levels of dietary cadmium intake for the general population. Studies from Sweden have shown a slow but steady increase in the cadmium content of vegetables over the years. The increase in body burden has been determined from an historic autopsy study (Friberg et al., 1986).

Toxicity. ***Acute Toxicity.*** Acute toxicity may result from the ingestion of relatively high concentrations of cadmium, as may occur in contaminated beverages or food. Nordberg (1972) relates an instance in which nausea, vomiting, and abdominal pain occurred from consumption of drinks containing approximately 16 mg per liter of cadmium. Recovery was rapid without apparent long-term effects. Inhalation of cadmium fumes or other heated cadmium-containing materials may produce an acute chemical pneumonitis and pulmonary edema.

Chronic Toxicity. The principal long-term effects of low-level exposure to cadmium are chronic obstructive pulmonary disease and emphysema and chronic renal tubular disease. There may also be effects on the cardiovascular and skeletal systems (Friberg et al., 1986).

Chronic Pulmonary Disease. Toxicity to the respiratory system is proportional to the time and level of exposure. Obstructive lung disease results from chronic bronchitis, progressive fibrosis of the lower airways, and accompanying alveolar damage leading to emphysema. The lung disease is manifested by dyspnea, reduced vital capacity, and increased residual volume. The pathogenesis of the lung lesion is the turnover and necrosis of alveolar macrophages. Released enzymes produce irreversible damage to alveolar basement membranes, including the rupture of septa and interstitial fibrosis. It has been found that cadmium reduces α-1-antitrypsin activity, perhaps enhancing pulmonary toxicity. However, no difference in plasma α-1-antitrypsin activity could be found between cadmium-exposed workers with and without emphysema (Lauwerys et al., 1979).

Cadmium Nephrotoxicity. The primary renal toxicity of cadmium affects proximal renal tubular function and is manifested by increased cadmium in the urine, proteinuria, aminoaciduria, glucosuria, and decreased renal tubular reabsorption of phosphate. Morphologic changes are nonspecific and consist of tubular cell degeneration in the initial stages, progressing to an interstitial inflammatory reaction and fibrosis. Analysis of kidney cadmium levels by in vivo neutron activation analysis and x-ray fluorescence has made it possible to study the relationship between renal cadmium levels and the occurrence of effects (Skerfving et al., 1987). The critical concentration of cadmium in the renal cortex that produces tubular dysfunction in 10 percent of the population is about 200 μg/g and is about 300 μg/g for 50 percent of the population. There is a pattern of liver and kidney cadmium levels increasing simultaneously until the average renal cortex cadmium concentration is about 300 μg/g and the average liver level is about 60 μg/g. At higher cadmium liver levels, the level in the renal cortex is disproportionately low, as cadmium is lost from the kidney (Ellis et al., 1984). Daily intake in food of 140–260 μg cadmium per day for more than 50 years or workroom air exposures of 50 μg/m^3 for more than 10 years have produced renal dysfunction (Thun et al., 1989; WHO, 1992). An epidemiological study of the dose–response relationship of cadmium intake from eating rice, using historical data, and β_2-microglobulinuria as an index of renal tubular dysfunction found that the total cadmium intake over a lifetime that produced an adverse health effect was 2000 mg for both men and women (Nogawa et al., 1989).

The proteinuria is principally tubular, consisting of low-molecular-weight proteins whose tubular reabsorption has been impaired by cadmium injury to proximal tubular lining cells. The predominant protein is a β_2-microglobulin, but a number of other low-molecular-weight proteins have been identified in the urine of workers with excessive cadmium exposure, such as retinol-binding protein, lysozyme, ribonuclease, and immunoglobulin light chains (Lauwerys et al., 1979). The presence of high-molecular-weight proteins in the urine, such as albumin and transferin, indicates that some workers may actually have a mixed proteinuria and suggests a glomerular effect as well. The pathogenesis of the glomerular lesion in cadmium nephropathy is not presently understood.

The Role of Metallothionein in Cadmium Toxicity. The accumulation of cadmium in the kidneys without apparent toxic effect is possible because of the formation of cadmium-thionein or metallothionein, a metal–protein complex with a low molecular weight (~ 6500) (Suzuki, 1982).

The amino acid composition of metallothionein is characterized by approximately 30 percent cysteine and the absence of aromatic amino acids. Specific optical absorption is due to the existence of metal–thiolate complexes in the protein. Metallothionein contains 61 amino acids and 20 are cys-

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teine. Structural studies using nuclear magnetic resonance spectroscopy and electron spin resonance spectroscopy have identified two distinct metal clusters in mammalian metallothionein. The clusters seem to have significant differences in their affinity for different metal ions; one of the clusters has a high level of specificity for zinc. Metal binding is by trimercaptide bridges (Boulanger et al., 1983). Metallothionein is primarily a tissue protein and is ubiquitous in most organs but it exists in the highest concentration in the liver, particularly following recent exposure, and in the kidneys, where it accumulates with age in proportion to cadmium concentration.

Cadmium bound to metallothionein within tissues is thought to be nontoxic; however, when the levels of cadmium exceed the critical concentration, it becomes toxic. The factors that determine the level of cadmium or of cadmium–metallothionein complex that is toxic are not clear, but experimental studies have shown that repeated injections of low levels of cadmium–metallothionein over several weeks results in a chronic and irreversible nephrotoxicity. Renal accumulations of cadmium were only 40 μg/g, less than the 200 μg/g suggested as the critical level in humans (Wang et al., 1993). Also, renal tubular necrosis occurs in non-cadmium exposed rats following transplantation of livers from cadmium toxic animals (Chan et al., 1993). These studies suggest that cadmium nephrotoxicity follows the slow release and renal excretion of cadmium–metallothionein from liver and other soft tissues. Cadmium–metallothionein is toxic when taken up by the proximal tubular cells complex whereas cadmium chloride at even greater concentrations in proximal tubular cells is not toxic (Dorian et al., 1995).

The Reversibility of Renal Effects. Follow-up studies of persons with renal tubular dysfunction (β_2-microglobulinuria) from occupational exposure to cadmium have shown that the proteinuria is irreversible and that there is a significant increase of creatinine in serum with time, suggesting a progressive glomerulopathy (Roels et al., 1989). Also, persons with renal tubular dysfunction from excess dietary ingestion of cadmium (cadmium-polluted rice) do not have a reversal of the defect as long as 10 years after reduced exposure in cases when the β_2-microglobulinuria exceeds 1000 μg per gram of creatinine (Kido et al., 1988). Ellis (1985) has shown, however, that liver cadmium in workers no longer exposed to cadmium gradually declines. Persistence of renal tubular dysfunction after cessation of exposure may reflect the level of body burden and the shifting of cadmium from liver to kidney.

The Skeletal System. Cadmium toxicity affects calcium metabolism, and individuals with severe cadmium nephropathy may have renal calculi and excess excretion of calcium, probably related to increased urinary loss, but with chronic exposure, urinary calcium may be less than normal. Associated skeletal changes are probably related to calcium loss and include bone pain, osteomalacia, and/or osteoporosis. Bone changes are part of a syndrome, Itai-Itai disease, recognized in postmenopausal multiparous women living in the Fuchu area of Japan prior to and during World War II. The syndrome consists of severe bone deformities and chronic renal disease. Excess cadmium exposure has been implicated in the pathogenesis of the syndrome, but vitamin D and perhaps other nutritional deficiencies are thought to be cofactors. Itai-Itai translates to "ouch-ouch," reflecting the accompanying bone pain. Also cadmium can affect calcium, phosphorous, and bone metabolism in both industrial workers and in people exposed in the general environment. These effects may be secondary to the cadmium effects on the kidneys, but there has been little study of calcium metabolism in people with excess exposure to cadmium. The increased prevalence of renal stones reported from certain industries is probably one manifestation of the cadmium-induced kidney effects. It is not known if certain factors other than cadmium may play a role.

Osteomalacia has been reported in a few heavily exposed industrial workers and in people with Itai-Itai disease. The industrial cases were mainly male, whereas Itai-Itai cases were almost exclusively female. However, the clinical features and biochemical findings are similar except that Itai-Itai patients may have osteoporosis as well.

Nogawa and colleagues (1987) reported that serum $1,25(OH)_2$ vitamin D levels were lower in Itai-Itai disease patients and in cadmium-exposed subjects with renal damage than in nonexposed subjects. A decrease in serum $1,25(OH)_2$ vitamin D levels was closely related to serum concentrations of parathyroid hormone. β_2-microglobulin and the percentage of tubular reabsorption suggest that cadmium-induced bone effects were mainly due to a disturbance in vitamin D and parathyroid hormone metabolism. Friberg and coworkers (1986) suggest that cadmium in the proximal tubular cells depresses cellular functions, which may be followed by the depressed conversion of 25(OH) vitamin D to $1,25(OH)_2$ vitamin D. This is likely to lead to a decreased calcium absorption and a decreased mineralization of bone, which in turn may lead to osteomalacia. Bhattacharyya and coworkers (1988) found, in studies of mice, that multiparity enhanced cadmium's toxicity to bone.

Hypertension and Cardiovascular Effects. Epidemiology studies suggest that cadmium is an etiological agent for essential hypertension. A recent study found an increase in systolic and diastolic blood pressures in cadmium workers. Only systolic, but not diastolic blood pressure, was significantly associated with cadmium dose in multivarate analyses (Thun et al., 1989). Studies from Japan have found a twice-as-high cerebrovascular disease mortality rate among people who had cadmium-induced renal tubular proteinuria as among people in cadmium-polluted areas without proteinuria (Nogawa et al., 1979).

Rats exposed to cadmium in drinking water (Kopp et al., 1983) developed electrocardiographic and biochemical changes in the myocardium and impairment of the functional status of the myocardium. These effects may be related to (1) decreased high-energy phosphate stored in the myocardium, (2) reduced myocardial contractility, and (3) diminished excitability of the cardiac conduction system. Jamall and Sprowls (1987) found that rats whose diets were supplemented with copper, selenium, and cadmium had a marked reduction in heart cytosolic glutathione peroxidase, superoxide dismutase, and catalase. They suggested that heart mitochondria are the site of the cadmium-induced biochemical lesion in the myocardium.

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Carcinogenicity. There have been a number of epidemiological studies intended to determine a relationship between occupational (respiratory) exposure to cadmium and lung cancer and prostatic cancer. A follow-up study of cadmium-nickel battery workers in Britain (Sorahan and Waterhouse, 1983) and in Sweden (Kjellström et al., 1979) found increased risks to lung and prostate cancer. An increase in respiratory cancers as also found in a re-study of a cohort in a U.S. cadmium recovery plant (Thun et al., 1985). Cadmium has recently been accepted by the International Agency for Research on Cancer as a Category 1 (human) carcinogen based primarily on its relationship to pulmonary tumors (IARC, 1994).

Animal studies have provided considerable support for the carcinogenic potential of cadmium. Cadmium chloride, oxide, sulphate, and sulphide produced local sarcomas in rats after their subcutaneous injection, and cadmium powder and cadmium sulphide produced local sarcomas in rats following their intramuscular administration. Cadmium chloride produced a dose-dependent increase in the incidence of lung carcinomas in rats after exposure by inhalation and a low incidence (5/100) of prostatic carcinomas after injection into the ventral prostate (Takenaka et al., 1983). While the evidence for a relationship between cadmium and cancer of the prostate in humans is debatable, more recent studies in rats have demonstrated carcinogenicity through the induction of cancer in the ventral prostate by oral or parenteral exposures, as well as by direct injection (Waalkes and Rehm, 1994).

Biological Indicators. The most important measure of excessive cadmium exposure is increased cadmium excretion in urine. In persons in the general population without excessive cadmium exposure, urinary cadmium excretion is both small and constant. That is, it is usually on the order of only 1 or 2 μg/day, or less than 1 μg/g creatinine. With excessive exposure to cadmium, as might occur in workers, an increase in urinary cadmium may not occur until all of the available cadmium binding sites are saturated. However, when the available binding sites (e.g., metallothionein) are saturated, increased urinary cadmium reflects recent exposure, body burden, and renal cadmium concentration, so that urinary cadmium measurement does provide a good index of excessive cadmium exposure. Nogawa et al. (1979) determined the urinary concentration of cadmium corresponding to a 1 percent prevalence rate of a number of abnormal urinary findings (Table 23-4). Tubular proteinuria, as indicated by measurable excretion of β_2-microglobulin, occurred at the 1 percent prevalence rate with a urinary cadmium concentration of 3.2 μg/g of creatinine. This was at a slightly lower urinary cadmium level than other signs of renal tubular dysfunction. Retinol binding protein may be a more practical and reliable test of proximal tubular function than β_2-microglobulin because sensitive immunological analytic methods are now available, and it is more stable in urine (Lauwerys et al., 1984). Changes in urinary excretion of low-molecular-weight proteins were consistently observed in workers excreting more than 10 μg cadmium per gram of creatinine (Buchet et al., 1980). Urinary excretion of *N*-acetyl-β-D-glucosaminidase (NAG) activity may be a sensitive indicator of cadmium-induced renal tubular dysfunction (Kawada et al., 1989), but a dose–response relationship has not been established.

Most of the cadmium in urine is bound to metallothionein, and there is good correlation between metallothionein and cadmium in urine in cadmium workers with normal or abnormal renal function. Therefore, the measurement of metallothionein in urine provides the same toxicological information as the measurement of cadmium and it does not have the problem of external contamination. Radioimmunoassay techniques for measurement of metallothionein are available (Chang et al., 1980).

Table 23–4
Urinary Cadmium Concentration Corresponding to 1 Percent Prevalence rate for Parameters of Renal Dysfunction

URINARY FINDING	URINARY CADMIUM μg/g CREATININE	
	Male	*Female*
Tubular proteinuria		
β_2-Microglobin	3.2	5.2
Retinal binding protein	4.4	7.4
Aminoaciduria (proline)	10.4	5.1
Proteinuria with glucosuria	7.4	7.4

SOURCE: Nogawa et al, 1979.

Treatment. Susceptibility to cadmium-induced toxicity is influenced by a number of factors, particularly the ability of the body to provide binding sites on metallothionein. Protection may be provided by induction of metallothionein by dietary zinc, cobalt, or selenium, but the only effective treatment for cadmium toxicity is to eliminate the exposure.

Chromium

Chromium is a generally abundant element in the earth's crust and occurs in oxidation states ranging from Cr^{2+} to Cr^{6+}, but only trivalent and hexavalent forms are of biological significance. The trivalent is the more common form. However, hexavalent forms of chromate compounds are of greater industrial importance. Sodium chromate and dichromate are the principal substances for the production of all chromium chemicals. Sodium dichromate is produced industrially by the reaction of sulfuric acid on sodium chromate. The major source of chromium is from chromite ore. Metallurgic-grade chromite is usually converted into one of several types of ferrochromium or other chromium alloys containing cobalt or nickel. Ferrochrome is used for the production of stainless steel. Chromates are produced by a smelting, roasting, and extraction process. The major uses of sodium dichromate are for the production of chrome pigments, for the production of chrome salts used for tanning leather, mordant dying, wood preservatives, and as an anticorrosive in cooking systems, boilers, and oil drilling muds. Overviews of chromium exposures and health effect have been reviewed (Fishbein, 1981; WHO, 1988; O'Flaherty, 1995).

Chromium in ambient air originates from industrial sources, particularly ferrochrome production, ore refining, chemical and refractory processing, and combustion of fossil fuels. In rural areas, chromium in air is usually less than 0.1

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